

- g. for any non-homologous import antibody amino acid residue which is expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence; and
- h. preparing a humanized antibody variable domain having amino acid sequences determined in steps a-g.

In claim 3, line 4, please delete "reasonably".

- 7. (Twice amended) A method for making a humanized antibody comprising providing an import antibody comprising a non-human antibody variable domain amino acid sequence which is desired to be humanized [(import antibody)] having a CDR and a FR, obtaining the amino acid sequence of [at least a portion of] a consensus human antibody variable domain of a human immunoglobulin subgroup, having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human antibody variable domain, and then substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:  
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
- 17. (Amended) A method of making a humanized antibody variable domain comprising the step of substituting Complementary Determining Region (CDR) amino acid residues of a variable domain of a non-human antibody for the corresponding CDR amino acid residues of [using] a consensus human antibody variable domain amino acid sequence of a human immunoglobulin subgroup [in the preparation of a humanized antibody].

19. (Amended) A method for making an improved antibody, comprising amino acid sequences from an import antibody comprising a non-human [(import)] antibody and a human antibody, comprising the steps of:
- a. obtaining the amino acid sequences of [at least a portion of] an import antibody variable domain and of a consensus human antibody variable domain of a human immunoglobulin subgroup;
  - b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human [amino] variable domain sequences;
  - c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
  - d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
  - e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
  - f. determining if the non-homologous import amino acid residue is [reasonably] expected to have at least one of the following effects:
    1. non-covalently binds antigen directly,
    2. interacts with a CDR; or
    3. participates in the  $V_L - V_H$  interface by affecting the proximity or orientation of the  $V_L$  and  $V_H$  regions with respect to one another;
  - g. for any non-homologous import antibody amino acid residue which is [reasonably] expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence[; and] ; and
  - h. preparing an improved, humanized antibody having amino acid sequences determined in steps a-g; and
  - i. evaluating the antigen binding or immunogenicity of the improved,